

Blood Clots, Thrombolytics, and the Emerging Role of the EndoWave Catheter

a report by

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Treatment for blood clots and their life-threatening sequelae has expanded significantly over the past 50 years. Thrombolytic therapy has gained widespread acceptance and use. Advances in technology have led to experiments with catheter-directed thrombolytic therapy in combination with other physical modality delivery systems, such as ultrasound, to improve the efficacy of thrombolytic therapy. One such thrombolytic ultrasound-guided therapy, the EKOS catheter system, will be reviewed in this article.

Thrombolytic Therapy

All available thrombolytic agents in clinical use today are plasminogen activators. These trypsin-like serine proteases have high specific activity directed at the cleavage of a single peptide bond in the plasminogen zymogen, converting it to plasmin. Plasmin is the active molecule that divides the fibrin polymer to thrombus dissolution. Due to the instability of plasmin at physiological pH, effective thrombolysis requires fibrin-bound plasminogen converted to its active form, plasmin, at the site of the thrombus.¹

The origin of thrombolytic therapy was the discovery by Tillet and Garner at Johns Hopkins Medical School in 1933 that certain strains of hemolytic streptococcal bacteria contained fibrinolytic properties.² Approximately 20 years later, Tillet first reported the intravascular administration of a thrombolytic agent, purified streptokinase. The experiment was

performed to obtain data on the safety of the administration of a thrombolytic agent in humans and was not used for the treatment of pathological thrombi. In 1957, Clifton at Cornell University Medical College in New York published his results of the first intravascular thrombolytic administration to treat occlusive thrombi. His study on the clinical effectiveness of a streptokinase–plasminogen combination in treating a wide range of pathological thrombi had frequent bleeding complications and inconsistent recanalization of blood vessels.³ Despite these results, however, Clifton is recognized as the first to use thrombolytic agents to treat pathological thrombi, as well as the first to use a catheter-directed administration for thrombolytic agents.

The Surgery or Thrombolysis for the Ischemic Lower Extremity (STILE) trial stands as supporting evidence for thrombolytic therapy. The STILE trial was a prospective, randomized analysis of thrombolysis versus surgery sponsored by Genetech (South San Francisco, CA), the manufacturer of the Activase brand of recombinant tissue plasminogen activator (rt-PA).⁴ A total of 393 patients with recent peripheral arterial occlusion were randomized to one of three treatment groups: rt-PA, urokinase, or primary operation. Although there was a slightly higher incidence of untoward events in the thrombolytic patients, the incidence of the end-points of amputation and death was equivalent between the groups. Subgroup analysis of the STILE data led to a further conclusion that patients with acute bypass graft occlusions treated with thrombolysis had significantly reduced amputation rates.⁵

With mounting evidence for the therapeutic benefits of thrombolytics, as exhibited in the STILE trial, technology has increased its efforts to improve the therapeutic potential of these agents. Based on the work from Trubestein et al. demonstrating the use of ultrasound energy for peripheral arterial clot dissolution in animal studies,⁶ ultrasound combined with thrombolytic agents was created as a potential therapeutic modality. The mechanism is derived from ultrasound increasing the transport of lytic enzymes into the thrombus. Ultrasound exposure leads to the disaggregation of large-diameter fibrin bundles into small-diameter bundles. The result is a reduction in flow resistance during ultrasound exposure, as well as enhanced fibrinolysis by exposing more binding sites for fibrinolytic agents.^{7,8}

EKOS EndoWave Catheter—Central Nervous System (CNS) and Non-CNS Applications

The EKOS EndoWave catheter system (EKOS Corporation, Bothell, WA) is a catheter-based drug delivery system utilizing high-frequency, low-power ultrasound. Its therapeutic applications include deep venous thrombosis



Biography

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(DVT), peripheral arterial occlusion, and acute cerebral infarction. For peripheral vessels, the EKOS Lysus system consists of a 5.2F catheter with a central lumen and three separate lumens for local infusion of a thrombolytic drug through small pores in the catheter. An ultrasound core wire located in the central lumen contains multiple miniature ultrasound transducers 1cm apart that deliver pulsed-wave ultrasound energy along the length of the catheter. For intracerebral arteries, the EKOS microinfusion system consists of a 0.014-inch catheter with an end-hold infusion lumen and a 1MHz transducer-tipped pulse-wave ultrasound element with a maximum power output of 120 Watts.

To date, there is a paucity of literature evaluating the EKOS catheter system. The majority of the EKOS literature studies treatment for acute stroke. Mahon et al. presented a safety study on using the EKOS MicoLysUS infusion catheter for acute embolic stroke treatment in North America. Fourteen patients aged 40–77 years with anterior- or posterior-circulation occlusion who presented with early symptom onset of cerebral ischemia were treated with the EKOS catheter and simultaneous intra-arterial thrombolysis. Their results stated an average recanalization time of 46 minutes. Nine patients survived, with eight of nine patients having significant improvements in their National Institutes of Health Stroke Scale (NIHSS) score. No catheter-related adverse effects occurred, leading to the conclusion that the EKOS system is feasible for the treatment of acute ischemic strokes, with future studies of its efficacy being warranted.⁹

The Interventional Management of Stroke (IMS) II Study further investigated the utility of the EKOS system. IMS II comprised 13 participating centers with 81 patients aged 18–80 years who received treatment with intravenous rt-PA within three hours of stroke symptom onset. For subjects with arterial occlusion at angiography after initial rt-PA infusion, additional rt-PA was infused via either a standard microcatheter or an EKOS catheter. Seventy-three percent of the EKOS-treated patients (22 of 33 patients) experienced recanalization compared with 56% (33 of 59 patients) in the group receiving the standard microcatheter without ultrasound. Notably, the rate of symptomatic intracerebral hemorrhage in IMS II subjects (9.9%) was not significantly different from that for tPA-treated subjects in the NINDS tPA Stroke Trial (6.6%). These positive results have prompted a follow-up IMS III trial with direct comparisons between microcatheters with and without ultrasound along with the MERCI concentric retrieval catheter.¹⁰

Non-central nervous system (CNS) applications of the EKOS system include occluded peripheral arteries, veins, and grafts. Wissgott et al. studied the safety and performance of the EKOS catheter in treatment for acute thrombotic or embolic occlusion of lower-limb arteries. From April 2005 to July 2006, the study enrolled 25 patients presenting with acute (<14 days old) occlusions in the lower-extremity arteries, and found 22 patients (88%) with total clot removal after approximately 16 hours. In two cases, clot removal was unable to be achieved and one patient had a bleeding complication due to dislocation of an introducer sheath. Two re-occlusions occurred at one-month follow-up.¹¹ These favorable results have led to further investigation of the EKOS catheter in peripheral arterial occlusion treatment.

There is only one published study involving the EKOS catheter and DVT. Between September 2004 and February 2006, Raabe et al. studied 40

Table 1: Comparison of Sample Patient, Indication, and Outcome Variables in Patients Undergoing Thrombolysis with a Standard Catheter and the EKOS EndoWave System

| | Standard Catheter (n=131) | EndoWave Catheter (n=21) |
|---------------------------|---------------------------|--------------------------|
| Patient | | |
| Male | 41% | 6.3%* |
| Hypertension | 63% | 62.5% |
| CAD | 33.3% | 32.5% |
| Diabetes | 28% | 25% |
| Indication | | |
| Arterial | 41.2% | 43.7% |
| Venous | 15.3% | 25.0% |
| Graft | 43.5% | 31.3% |
| Outcome | | |
| Success | 85.8% | 100% |
| Total rt-PA dose (mg) | 40.8±4.3 | 13.5±4.5* |
| Lowest fibrinogen (mg/dl) | 239±16.2 | 274±31 |

* *p*<0.05 compared with standard catheter.
CAD = coronary artery disease; rt-PA = recombinant tissue plasminogen activator.

patients with a combined 45 DVTs in the upper and lower extremities treated with various thrombolytics and the EKOS catheter. Seventy-one percent of the EKOS cases had >90% angiographic lysis and 20% had partial lysis. These results were compared with those of the National Venous Thrombolysis Registry, in which only 31% of patients had complete lysis and 52% had partial lysis. The average time for complete lysis using the EKOS system was 24.7 hours compared with 53.4 hours in the National Venous Thrombolysis Registry.¹²

Wissgott et al. compared the safety and effectiveness of a mechanical thrombectomy system with the EKOS ultrasound thrombolysis in acute occlusion of femoropopliteal bypass grafts. Twenty patients with acute bypass graft occlusions were enrolled from April 2005 to March 2007 and treated with thrombectomy (n=10) or ultrasound thrombolysis (n=10). Results showed technical success in 100% of the thrombectomy group compared with 90% in the lysis group. Mean treatment time was significantly shorter: 64.5 minutes (range 45–90 minutes) in the thrombectomy group compared with 904.0 minutes (range 120–1,350 minutes) in the lysis group. Both groups demonstrated improved ankle brachial index (ABI) at discharge and at one-month follow-up. One lysis case was discontinued secondary to dislocation of the introducer sheath. The study concluded that both methods were effective treatment options for acute femoropopliteal bypass graft occlusions, with mechanical thrombectomy restoring blood flow much faster.¹³

The East Carolina University Experience

The authors’ practice is a tertiary vascular practice at a high-volume rural academic center. Over the past several years, the cardiovascular operators have adopted an aggressive stance toward endovascular therapy and have taken on the endoluminal care of the vascular patients under their care. We were intrigued by the EKOS catheter system, primarily because of the possibility of reducing the total amount of thrombolytic required to achieve successful thrombolysis. Our center has been using the system since its approval by the US Food and Drug Administration (FDA), and thus far we have had excellent results with an efficacy comparable to that of a traditional fountain-style thrombolytic system. At our facility, rt-PA is the

lytic agent of choice. Patients undergoing lytic therapy at our medical center are admitted to the intensive care unit and undergo close serial observation for local and systemic bleeding complications. Serial serum fibrinogen levels are determined, and the lytic therapy is halted if the absolute fibrinogen level is <150mg/dl or there is a drop of >200mg/dl from the baseline fibrinogen level.

The authors' hypothesis is that use of the EndoWave system will result in a lower dose of rt-PA with a comparable technical success rate. For the purposes of this review, success was defined as complete removal of thrombus and identification of the underlying anatomical situation that caused the occlusion. Under the auspices of an Institutional Review Board-approved study, a retrospective review over the past three years (2005–2008) was undertaken. Using appropriate common procedural terminology (CPT) codes to query a billing database, cases were identified. Variables were collected, including demographic and clinical variables potentially associated with the end-points of success and total rt-PA dose. A summary of the results is shown in *Table 1*. Additional variables were collected, but are omitted from this article for the sake of brevity. There was a gender difference, but otherwise no significant differences were seen in the patient, clinical, or indication variables collected. Our hypothesis—that the EKOS system would allow a similar efficacy with a lower dose of thrombolytic—was supported by this analysis. Of course, the sample size is small, but these data are promising and support the use of the system in order to improve patient safety.

Conclusions

Thrombolytic therapy is an indispensable part of the vascular provider's armamentarium. Successful results can be obtained via a variety of catheter-based systems. The EKOS EndoWave system has the added advantage of improved thrombus penetration via the use of an ultrasound wave. This improved thrombus penetration has resulted in faster lytic therapy times and lower doses of thrombolytic agents. In theory, both of these factors will translate into a lower incidence of adverse events and improved patient safety, while maintaining efficacy. ■

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